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CURES FOR INFECTIOUS DISEASES.

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CURES FOR INFECTIOUS DISEASES.

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Our knowledge of the nature of the conflict between the organism and the microbe has now so far advanced that, of the numerous "cures" that have been attempted, a partial explanation of the *modus operandi* of the curative agents can in many cases be brought forward. Such "cures" can be roughly divided into two classes; (*a*) those in which a "febrile reaction" is probably produced, and (*b*) those in which a bactericidal substance is introduced into the living animal body.

Of the first of these classes a good example is to be found in Buchner's method of curing anthrax by injection of sterilised cultures of bacillus pneumoniæ.[1] The living anthrax microbe and the sterilised pneumonia culture were subcutaneously injected in different parts of the body, in order to exclude as far as possible the direct action of one upon the other. About 50 per cent. of rabbits treated in this way completely recovered. It was found that the sterilised cultures of Friedländer's pneumonia bacillus produced a rise of temperature when injected into healthy rabbits, and not only this but also other febrile symptoms when injected into the experimenter himself. In 1887 Emmerich[2] succeeded in making rabbits refractory to anthrax by inoculation with the erysipelas microbe. Probably here again a stimulation of the febrile reaction occurs. In a certain number of cases I have succeeded in curing rabbits of anthrax by injections of minute quantities of

[1] Buchner: Ueber Hemmung der Milzbrand Infection und ueber das aseptische Fieber, *Berliner klinische Wochenschrift*, 1890, No. 10.
[2] Emmerich: *Archiv für Hygiene*, vol. vi., 1857, p. 442.

pepsin or trypsin.[3] Hildebrandt[4] has lately shown that these substances, besides various poisonous symptoms, produce a rise of temperature.

It is well known that if rabbits are inoculated with very virulent anthrax, as a rule no rise of temperature takes place, and the animal dies within a couple of days. Inoculation with less virulent anthrax is often attended with a rise of temperature, and the animal may only succumb after a longer struggle with the microbe. Only if the rabbits have been made immune against anthrax is an inoculation with the virulent bacillus followed by a rise of temperature. I have found that when the animal's power of resisting the onset of the disease has been increased by injecting a "protective proteid," a febrile reaction occurs, and on the death of the animal the bacilli showed various signs of degeneration.

In all these cases it appears that the increased power of resisting the attack of a pathogenic microbe is attended with the appearance of a "febrile reaction." What is the nature of this "febrile reaction?" A great many speculations and but few facts have been brought forward to explain its action.[5]

It has been supposed that the temperature *per se* exercised a harmful action on the microbes present. Bouchard[6] has shown that this explanation does not hold. He once found virulent anthrax bacilli in a rabbit, in which a rise of temperature to 44° C had intervened between its inoculation and death, which temperature would be amply sufficient to attenuate, and even kill the same bacilli when growing in a test tube.

The following experiment of my own appears to throw some light on the subject, and indicates another way of arriving at an explanation of fever. A rabbit was inoculated with anthrax; twenty-four hours afterwards it was found to have a temperature of 40.4°. It was then decapitated, and its blood allowed to flow into alcohol. After some days the precipitated proteids were filtered off, dried,

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[3] Hankin: A New Result of the Injection of Ferments, *Proceedings of the Cambridge Philosophical Society*, November 11th, 1889, vol. vii., p. 16.

[4] *Virchow's Archiv*, vol. 122, p. 1.

[5] See the Goulstonian Lectures on the Nature of Fever, by Dr. Donald MacAlister, Fellow of St. John's College, Cambridge. (London: Macmillan and Co., 1887).

[6] *Actions des Produits sécrétés par les Microbes Pathogènes.* Paris: Gautier Villars et Fils, 1890.

and extracted with water. The extract was filtered, and it was found to have the power of killing anthrax bacilli. This was tested by the plate culture method as used by Nissen, Nuttal, and Buchner. In several other experiments I equally succeeded in extracting a bacteria-killing substance from febrile blood. From normal blood, on the contrary, I could not by this method prepare a solution having bactericidal powers, except in one or two cases, and then to a very slight degree.[7]

From these experiments it may be surmised that the "febrile reaction" is in some way connected with the appearance of bacteria-killing substances in the blood ; certain researches that have recently been published give good ground for hoping that the investigation of such "natural disinfectants" will lead to valuable practical results. Foremost among these researches must be mentioned the work of Behring and Kitasato on tetanus and diphtheria[8]. These investigators have succeeded in curing the above-mentioned diseases by injections of serum from animals that had previously been made immune against the tetanus and diphtheria bacilli. In this case, however, the serum appears to owe the curative power to a substance that destroys the poison produced by the microbes rather than the microbes themselves.

Other researches recently published show that the serum of naturally immune animals can be used to confer insusceptibility to a disease. Behring,[9] in an article on Disinfectants in the current number of the *Zeitschrift für Hygiene*, mentions that he has made mice immune against anthrax by injections of rats' serum. Ogata and Jasuhara have recently published in the *Proceedings of the University of Tokio* (Japan) a paper entitled "The Influence Exerted by the Blood of Various Animals on the Anthrax Bacilli." They have succeeded in curing mice from attenuated anthrax by injections of blood from dogs, rats and frogs.

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[7] Hankin : Indications for the Cure of Infectious Diseases, read at the Leeds meeting of the British Association for the Advancement of Science, 1890.

[8] Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Theiren, *Deutsche medicinische Wochenschrift*, No. 49, December 4th, 1890, p. 1113 ; also Hankin : "A Cure for Tetanus and Diphtheria," *Nature*, December 11, 1890, p. 121.

[9] Ueber Disinfection und Disinfectionsmittel, *Zeitschr. f. Hygiene*, vol. ix., 1890, p. 473.

They found it necessary to inject the blood within five hours after inoculation. I have recently obtained similar results by injections of rats' serum, and have found that the injection of so small a quantity of serum as 0.01 cubic centimetre was sufficient to preserve a mouse from exceptionally virulent anthrax. In one experiment eight mice were inoculated with rats' serum in quantities varying from 0.01 to 0.11 cubic centimetre, and in the same place with virulent anthrax spores. All of them remained in good health, while two control mice died within eighteen hours.

That this result is not due to a "febrile reaction" was shown by another experiment in which ten mice were used, and in which the serum and spores were injected at different parts of the body. In this way the direct antiseptic action on the anthrax spores was diminished, and in this experiment every mouse died, though from one to three days later than the controls. The latter, as in the other experiment, died within eighteen hours.

What are the substances to which these curative actions are due? Apparently they belong to a class of bodies which I have called "protective proteids," and which I described in this Journal[10] nearly a year ago. By the methods described in the article referred to I have isolated the protective proteid from both the spleen and blood serum of the rat, and with it I have succeeded in rendering mice insusceptible to anthrax.

I find that this substance is a globulin which (so far as I know) stands alone among bodies of this class in giving an alkaline reaction, even after prolonged dialysis against normal salt solution. Since it is only soluble in dilute salt solutions, the alkaline reaction vanishes by dialysis against distilled water, to return on the addition of a small quantity of pure sodium chloride. A further account of my experiments with the rat's defensive proteid will shortly appear in the *Centralblatt für Bakteriologie*.

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[10] *British Medical Journal*, July 12th, 1890, "On the Conflict between the Organism and the Microbe;" also "A Bacteria Killing Globulin," *Proceedings of the Royal Society of London*, May 21, 1890, vol. 48, p. 93.